UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DEC 22 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Assure: Reevaluation of the uterine effects seen in 6-months feeding study in dogs

Caswell No. 215D

TO: Robert Taylor / V. Walters, PM (25)
Registration Division (TS-767c)

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INTRODUCTION: Groups of dogs (6/sex/dose) were fed Assure (99.1% pure) at dietary concentrations of 0, 25, 100, and 400 ppm for 6 months. The results of this study were previously evaluated by a reviewer, and he concluded that the decrease in uterine weight and number of corpora lutea in 100 ppm females were compound-related (Table 1)(Tox. Document No. 004589). Based upon these observations, the LEL for the subchronic toxicity of Assure in dogs was previously established as 100 ppm; NOEL, 25 ppm (previous DER attached).

DISCUSSION: The results of this study have been reevaluated. It was determined that the data presented in Table 1 do not equivocally demonstrate that the decreases in uterine weight and total number of corpora lutea in 100 ppm females were compound-related for the following reasons:

1). Uterine weight in female animals depends on the time of sacrifice relative to the estrous cycle. It appears that the estrous cycle of most female dogs at 100 ppm could be different from that of the animals in other groups.

2). The decreases in uterine weight and total number of corpora lutea seen in 100 ppm females were not found in 400 ppm femles. On the contrary, these parameters were increased relative to those of the controls.

3). The changes in the uterine weight and number of corpora lutea were not seen in Assure treated females of a 1-year dog feeding study at similar dose levels (Tox. Document No.005030).

In the 6-month study, there was an increased incidence of testicular atrophy in 400 ppm males (2/6) relative to the controls. This incidence was also seen in oncogenicity and subchronic feeding studies in mice. Therefore, it would be more appropriate in establishing the LEL at 400 ppm; NOEL, 100 ppm.

Table 1*

Uterine Weights and Corpora Lutea in 6-Month Assure Treated Female Dogs

Dose (ppm)	0	25	100	400
No. Examined	6	6	6	6
Uterine weights	5.0±2.9	6.7±2.5	2.7±0.3	13.6±3.9
Corpora lutea	5-1	Oi	0	Oi
	Oi	4-0	0	2-2
	Oi	2-4	5-6	5-3
	3-3	0	0	5-3
	Oi	3-3	0	3-6
	2-2	0	0	2-4
Total No. of Corpora lutea	16	16	11	32

* Data taken from the previous DER (Tox. No. 004589)

Oi: immature ovary and no corpora lutea

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TOXICOLOGY BRANCH DATA REVIEW

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Study Type: Six-months feeding study in dogs.

Accession No.: 250553, replacement for 250074

MRID No.:

Sponsor: DuPont

Contracting Lab: Nissan Chem. Ind. Ltd.

Date: April 28, 1983

Test Material: 2-[4-(6-Chloroquinoxalin-2-yloxy)-phenoxyl]-, ethyl ester (99.1%).

DPX-Y6202, NC302.

Protocol:

The following table indicates the design of this six-months feeding study in 5 months old dogs.

Group of administration	No. of Animals used		Animal No.	
	Male	Female	Male	Female
0 ppm	6	6	1101-1106	2101-2106
25 ppm	6	6	1201-1206	2201-2206
100 ppm	6	6	1301-1306	2301-2306
400 ppm	6	6	1401-1406	2401-2406
Total	24	24		

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Results:

No dogs died during the feeding.

Interstitial pneumonia was present in every animal. Ovaries and uteri tended to decrease in absolute weight and in relative organ to body weights of females in the 100 ppm group. The same values increased at the 400 ppm level as shown in the following table.

	Control	25 ppm	100 ppm	400 ppm
Absolute uterus weights	0.50 ± 2.85	6.73 ± 2.46	2.67 ± 0.27	13.16 ± 3.9
Percent of body weights	0.06 ± 0.02	0.06 ± 0.02	0.03 ± 0.02	0.10 ± 0.0

The incidence of corpora lutea (shown below) correlates with uterus weights.

	0	25 ppm	100 ppm	400 ppm
Corpora lutea	5-1	0i	0	0i
	0i	4-0	0	2-2
	0i	2-4	5-6	5-3
	3-3	0	0	3-2
	0i	3-3	0	3-6
	2-2	0	0	2-4
Total	16	16	11	32

The incidence of corpora lutea is shown separately for each overy.

0i indicates immature ovaries and no corpora lutea.

Testicular atrophy was seen in 2 of 6 males in the 400 ppm group and testicular infection in another of the same group.

Conclusions:

NOEL 25ppm
LEL 100ppm

Core classification:

Guideline.

DCR-10638:W.ThomasEdwards:TOX-27:Rm824:CM-2:557-1511:7/29/83:efs